

**Rationale, design, and baseline characteristics of the SIGNIFY trial:  
a randomized, double-blind, placebo-controlled trial of  
ivabradine in patients with stable coronary artery disease  
without clinical heart failure**

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## **Abstract** (250 words)

**Background.** Elevated heart rate in stable coronary artery disease (CAD) is associated with worse outcomes, particularly increased risk of myocardial infarction. Heart rate reduction with the  $I_f$  inhibitor ivabradine confers symptomatic benefits in angina pectoris, and reduces coronary events in patients with stable CAD and left ventricular (LV) systolic dysfunction with resting heart rate  $\geq 70$  bpm. SIGNIFY is testing the hypothesis that heart rate reduction using ivabradine reduces mortality and cardiovascular events in patients with stable CAD, but without clinical heart failure.

**Methods** SIGNIFY is a randomized, double-blind, parallel-group, placebo-controlled, event-driven study in patients with stable CAD (1139 centers, 51 countries). Participants are aged  $\geq 55$  years, with stable CAD and LV ejection fraction  $>40\%$ , in sinus rhythm, with baseline resting heart rate  $\geq 70$  bpm, and with at least one additional cardiovascular risk factor. At inclusion, patients receive ivabradine 7.5 mg bid or matching placebo, which is adjusted at every visit to a heart rate target of 60 bpm. Participants should receive the best possible background treatment for stable CAD. The primary endpoint is a composite of cardiovascular death or nonfatal myocardial infarction.

**Results** Recruitment lasted from October 2009 to April 2012. SIGNIFY has recruited 19 102 patients (age  $65.0 \pm 7.2$  years, resting heart rate  $77.2 \pm 7.0$  bpm, 72% male) with no evidence for LV dysfunction (ejection fraction,  $56.5 \pm 8.6\%$ ).

**Conclusion** SIGNIFY is expected to shed further light on the role of heart rate lowering with ivabradine in patients with stable CAD without clinical heart failure. The study is expected to end in 2014.

## Introduction

Coronary artery disease (CAD) is highly prevalent and affects between a quarter and a third of the population aged >60 years.<sup>1</sup> Despite major advances in therapy in the last four decades, which have contributed to substantial declines in both morbidity and mortality, patients with stable CAD still have poor outcomes, possibly due to unfavorable trends in some risk factors, such as rising obesity and diabetes<sup>2</sup> or increased prevalence of smoking among younger women. Elevated heart rate has been shown to be a risk marker in the general population and in patients with cardiovascular disease,<sup>3-6</sup> and is now recognized as a modifiable risk factor in heart failure.<sup>7</sup> In line with this, current guidelines recommend reducing resting heart rate to 55 to 60 bpm for the prevention of ischemia and angina in patients with chronic stable angina.<sup>8</sup> The ongoing SIGNIFY (Study assessing the morbidity–mortality beNefits of the  $I_f$  inhibitor ivabradine in patients with coronarY artery disease) trial was designed to test the hypothesis that heart rate lowering with ivabradine reduces cardiovascular event rates in patients with stable CAD. In this article, we describe the rationale and design of SIGNIFY, as well as the baseline characteristics of the population.

## Rationale

Elevated heart rate has a range of negative pathophysiological effects in stable CAD, all of which contribute to the development and progression of the disease.<sup>3,4</sup> Increased heart rate is associated with an imbalance in myocardial oxygen supply and demand, with increased oxygen consumption and decreased perfusion time. These effects may lead to myocardial ischemia, which manifests as angina pectoris or myocardial infarction (MI). Beyond myocardial ischemia, elevated heart rate may have a direct impact on the arterial wall, exerting local hemodynamic forces with an adverse effect on the endothelium due to increased exposure to cyclical stress. This increases arterial stiffness and promotes atherosclerosis. High heart rate has been associated with increased risk of coronary plaque disruption,<sup>9</sup> possibly because elevated heart rate increases exposure to low shear stress, which is a powerful local

stimulus for the development and progression of early stable atherosclerotic plaque to high-risk vulnerable plaque. Continued altered shear stress can lead to expansive vascular remodeling and plaque progression with intensive lipid accumulation, inflammation, and a thin fibrous cap. Endothelial shear stress plays a prominent role in the atherogenic process, as confirmed by a recent report of the changes in coronary plaque and arterial remodeling in acute coronary syndrome patients.<sup>10</sup> This report was particularly striking since the observations were made in CAD patients followed clinically over 1 year after their acute coronary syndrome, during which time they were aggressively managed with vasculoprotective agents. Finally, since wall motion is highest at high heart rates, this increases the exposure of vulnerable plaque to these detrimental stresses, making the coronary arteries even more susceptible to plaque rupture.<sup>9</sup> These effects combine to increase the risk for adverse clinical outcomes in CAD.

The relationship between elevated heart rate and events in stable CAD appears to be particularly strong for MI, as was first documented in patients with CAD and LV dysfunction in BEAUTIFUL (morBidity-mortality EvAlUaTion of the  $I_f$  inhibitor ivabradine in patients with coronary disease and left-ventricULar dysfunction).<sup>11</sup> In the placebo group of that study, patients with heart rate  $\geq 70$  bpm were at 46% greater risk for fatal and nonfatal MI ( $p=0.0066$ ) and a 34% greater risk for cardiovascular death ( $p=0.0041$ ) than patients with heart rate  $< 70$  bpm. BEAUTIFUL suggested that heart rate 70 bpm is a potential threshold above which patients with stable CAD are at higher risk of cardiovascular events.

Lowering heart rate may therefore be expected to reduce mortality and cardiovascular event rates in patients with stable CAD.<sup>5-12</sup> So far, this has proved difficult to demonstrate, partly because most agents that lower heart rate, such as  $\beta$ -blockers and non-dihydropyridine calcium channel blockers, also have other cardiovascular effects, which may be confounding factors. The  $I_f$  inhibitor ivabradine lowers heart rate via specific modulation of the activity of the pacemaker cells in the sinoatrial node, and has no direct effect on other cardiac parameters, notably myocardial contractility, cardiac output,<sup>13</sup> and coronary hemodynamics. In the

clinical setting, heart rate reduction with ivabradine confers symptomatic benefits in patients with angina pectoris, in monotherapy and in combination with  $\beta$ -blocker therapy,<sup>14,15</sup> and has been demonstrated to improve prognosis in chronic systolic heart failure.<sup>16</sup>

As regards prognosis in stable CAD, although treatment with ivabradine did not affect the primary endpoint overall in the BEAUTIFUL trial, it did reduce coronary events in a prespecified subgroup of patients with stable CAD and LV systolic dysfunction and elevated heart rate ( $\geq 70$  bpm).<sup>17</sup> The reduction in coronary events with ivabradine was particularly marked in a post hoc analysis of BEAUTIFUL patients with limiting symptoms of angina pectoris at baseline (equivalent to Canadian Cardiovascular Society [CCS] classes II and III).<sup>18</sup> On the other hand, ivabradine's prognostic benefits in CAD patients without LV systolic dysfunction have never been formally tested. The SIGNIFY study was set up with the hypothesis that heart rate-lowering with ivabradine would reduce mortality and cardiovascular events in patients with stable CAD, but without clinical heart failure.

### **SIGNIFY study design**

SIGNIFY is an international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, event-driven study in patients with stable CAD. The study is ongoing in 1139 centers in 51 countries worldwide. The study is being performed according to the principles laid out in the Declaration of Helsinki (1964, and its text revisions), and approval has been obtained from ethics committees in all countries concerned. SIGNIFY is registered on [www.controlled-trials.com](http://www.controlled-trials.com) (ISRCTN61576291).

The main inclusion and exclusion criteria are listed in **Table 1**. Participants were aged  $\geq 55$  years with documented stable CAD, but no evidence of heart failure (LV ejection fraction  $>40\%$ ). Participants had to be in sinus rhythm with resting heart rate  $\geq 70$  bpm measured by standard 12-lead electrocardiography (ECG) in two consecutive recordings performed  $>5$  minutes apart. They also had at least one major or two minor cardiovascular risk factors (**Table 1**). Patients could be excluded at the end of

run-in, if they had an unstable cardiovascular condition, had compliance of <70% during placebo run-in, or failed to confirm eligibility. All participants gave written informed consent.

After a single-blind run-in period of 14 to 30 days with placebo, eligible patients were randomly allocated to receive ivabradine or placebo; randomization was carried out via an interactive response system (voice or web). The double-blind period is expected to last between 18 and 48-60 months, and the study plan includes visits at 1, 2, 3, and 6 months, and at 6-monthly intervals thereafter (**Figure 1**).

At inclusion, patients received ivabradine 7.5 mg bid or matching placebo, except for patients aged  $\geq 75$  years, who were initiated at 5 mg bid. At every subsequent visit, resting heart rate is measured by 12-lead ECG (two consecutive recordings performed >5 minutes apart) and the study treatment adjusted accordingly with a target heart rate of 60 bpm. Thus, patients with heart rates >60 bpm receive the next highest dosage (maximum 10 mg bid or matching placebo); patients with heart rates 50 to 60 bpm are maintained on the same dosage; and patients with heart rates <50 bpm or with signs or symptoms of bradycardia receive the next lowest dosage (minimum 5 mg bid or matching placebo). In patients already on 5 mg bid, study treatment is stopped if heart rate is <45 bpm or if there are signs or symptoms of bradycardia. Patients with heart rate between 45 and 50 bpm on 5 mg bid and no signs or symptoms of bradycardia are invited for a control visit within 1 week and then stop study drug if heart rate remains <50 bpm. Patients and investigators are blinded to treatment allocation, and study drug and placebo have identical appearance, though the actual dosage of ivabradine or matched placebo is not blinded.

All participants are expected to be treated with guidelines-directed background cardiovascular medication. The dosage of background therapy (notably,  $\beta$ -blocker) should be optimized prior to selection, and investigators are encouraged to make every effort to keep it stable throughout the study. Prohibited treatments include strong cytochrome P450 3A4 inhibitors, such as some macrolide antibiotics,

antiretroviral drugs (e.g. ritonavir, nelfinavir), systemic azole antifungal agents, and nefazodone. Treatments known to increase the QT interval are not recommended with ivabradine and should be monitored carefully if administered concomitantly. Other heart rate–lowering agents (e.g.,  $\beta$ -blockers and non-dihydropyridine calcium channel blockers) are allowed, but introduction of such an agent after the beginning of the study is discouraged unless clinically indicated.

The investigation schedule is shown in **Figure 1**. Baseline assessments include verification of inclusion criteria, record of medical history, clinical examination, concomitant treatments, and smoking habits; evaluation of cardiac parameters (resting heart rate [ECG], CCS class, New York Heart Association [NYHA] class, supine blood pressure, and LV ejection fraction [echocardiography]); measurement of laboratory parameters (blood sample); and recording of adverse events. All of these parameters are measured at every subsequent visit, with the exception of LV ejection fraction (baseline only), laboratory parameters (at 3 and 12 months, and at yearly intervals thereafter), and smoking habits (yearly intervals). Compliance is measured at every post-baseline visit by tablet counts.

The primary endpoint of SIGNIFY is a composite of cardiovascular death or nonfatal MI. Secondary endpoints include: all-cause death, cardiovascular death, coronary death, nonfatal MI, coronary revascularization, elective coronary revascularization, and new onset or worsening heart failure. There are also six secondary composite endpoints: fatal or nonfatal MI; fatal or nonfatal MI or coronary revascularization; fatal or nonfatal MI, coronary revascularization, or unstable angina; cardiovascular death, nonfatal MI, or nonfatal stroke; coronary death or nonfatal MI; and nonfatal MI, coronary revascularization, or unstable angina. These outcomes will be analyzed on a time-to-first event basis. All endpoints are adjudicated by an independent Endpoint Validation Committee (definitions of endpoints used by the adjudicators are provided in supplementary material).

## **SIGNIFY study organization**

The Executive Committee is responsible for the development of the protocol and its amendments, and the scientific and clinical conduct of the study. The Steering Committee represents the trial investigators and comprises the national study coordinators. They approve the protocol and its amendments. The Endpoint Validation Committee reviews and adjudicates all pre-specified endpoints using blinded data according to definitions laid out in a charter. The Independent Data Monitoring Committee evaluates unblinded efficacy and safety data during the study. Members of the committees are listed in the Appendix at the end of this paper.

## **Statistical issues**

Randomization was stratified by center and angina status (whether or not patients were CCS class II or higher). 1070 primary events are necessary to detect a difference between the time to first primary endpoint distributions of placebo and ivabradine groups, assuming a 5% type I error rate, 90% power, and an expected relative risk reduction of 18%. A sample size of 11 330 patients was initially considered sufficient to reach this target assuming an annual incidence of the primary composite endpoint of 4.5% in the placebo group and a mean follow-up of 2.5 years. Blinded interim evaluation in the overall population was carried out in June 2011 and this indicated that the annual incidence of the primary composite endpoint was around 2.5% giving an estimate of 2.7% in the placebo group on the assumption of a relative risk reduction of 18%. On the basis of this revised incidence, the sample size was revised to 16 850 patients and the recruitment period was extended (2.5 years instead of 2 years) giving, with the desired minimal follow-up of 18 months, an expected mean follow-up duration of 2.75 years. This sample size takes into account the non-cardiovascular deaths and consent withdrawals (same initial assumptions of annual overall incidence of 1% for each event). The actual mean duration of follow-up may be extended or reduced to achieve the planned number of events.



The main analysis will be based on the intention-to-treat principle, and in terms of time to first event. The superiority of ivabradine versus placebo will be tested on the primary composite endpoint using a Cox's proportional hazard model, adjusted for the presence of angina pectoris at baseline (CCS class II or higher). The type I error will be set at 5% (two-sided) for all statistical tests, and estimates of hazard ratios and 95% confidence intervals will be provided. Similar analyses will be performed for the individual components of the primary composite endpoint, as well as the secondary endpoints. Analyses are also planned in a subgroup of the population with angina pectoris at baseline (CCS class II or higher).

Baseline characteristics are summarized as mean (standard deviation) for continuous variables and count (percentage) for categorical variables. All analyses will be performed on adjudicated endpoints. Statistical analyses will be performed by the independent Robertson Centre for Biostatistics, University of Glasgow, UK.

In addition to reviewing the efficacy and safety data, the Data Monitoring Committee will conduct two formal interim analyses to determine if there is overwhelming evidence for benefit or harm that might require the study to be terminated prematurely. These analyses will take place when 35% and 60% of the expected primary endpoint events have occurred. A recommendation for early termination of the study on the basis of benefit will be considered if ivabradine is superior to placebo on the primary endpoint with a two-sided p-value  $\leq 0.001$ .

### **SIGNIFY substudies**

The SIGNIFY study has three planned substudies:

- The *Quality of Life Substudy* plans to evaluate changes in the Seattle Angina Questionnaire in 4500 patients with angina pectoris at baseline (CCS class II or higher).
- The *Biomarkers Substudy* has the objective of detecting changes in circulating von Willebrand factor, as well as high-sensitivity troponin T and other

biomarkers of CAD progression and endothelial function, in a group of 380 patients.

- The *Pharmacogenomics Substudy* will analyze whether genetic variations in candidate genes and in the whole genome are associated with clinical outcomes in about 5000 patients.

### **Baseline characteristics**

Recruitment into SIGNIFY started in October 2009 and the last patient was randomized in April 2012. The baseline characteristics of the 19 102 randomized patients included in the trial are presented in **Table 2**. The mean age of the randomized population was  $65.0 \pm 7.2$  years with a mean resting heart rate of  $77.2 \pm 7.0$  bpm, and 72% of the participants were male. In terms of cardiovascular risk factors, a considerable proportion of the population had angina pectoris (CCS class II or higher) (63%) or a history of MI (73%). About a quarter of the population were current smokers (24%). A large proportion had other cardiovascular risk factors, notably hypertension (86%), dyslipidemia (71%), or diabetes mellitus (43%). In line with the inclusion criteria, a substantial proportion of the population cumulated risk factors, for instance, 22% had both diabetes and angina pectoris (CCS class II or higher). There was no evidence for LV systolic dysfunction (mean ejection fraction,  $56.5 \pm 8.6\%$ ) or clinical heart failure. The SIGNIFY population was well treated in terms of background cardiovascular medication at baseline, particularly for antithrombotic agents (98%), statins (92%), angiotensin-converting enzyme inhibitors (59%), angiotensin receptor blockers (23%), and  $\beta$ -blockade (83%).

### **Discussion**

SIGNIFY has enrolled a population of patients with stable CAD, resting heart rate  $\geq 70$  bpm and LV ejection fraction  $>40\%$ , and with no evidence for heart failure, but with relatively high rates of cardiovascular risk factors, most notably hypertension (86%), angina pectoris (63%), diabetes (43%), and current smoking (24%). This is a particularly relevant population in the light of the known beneficial impact of

ivabradine in patients with stable CAD, LV dysfunction, and heart rate  $\geq 70$  bpm in BEAUTIFUL,<sup>17</sup> as well as in a subgroup of BEAUTIFUL patients with angina pectoris.<sup>18</sup> Furthermore, recent observational studies, the EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events)<sup>19</sup> and COURAGE (Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation),<sup>20</sup> reported that cardiovascular risk factors remain highly prevalent in patients with stable CAD, and also that there is imperfect achievement of risk factor control. Resting heart rate stands as an easily modifiable parameter that could improve risk assessment and management of patients with cardiovascular disease.

The characteristics of the SIGNIFY population are broadly similar to those of patients included in international registries in CAD. The SIGNIFY population is comparable to the CAD population in REACH (REduction of Atherothrombosis for Continued Health)<sup>21</sup> and patients with heart rate  $\geq 70$  bpm in the CLARIFY (prospective observational Longitudinal Registry of patients with stable coronary artery disease) registry,<sup>22</sup> though they are generally of higher risk (for example, higher rates of smoking, angina, hypertension, and diabetes), in line with SIGNIFY inclusion criterion of additional cardiovascular risk factors. Similarly, differences between the characteristics of the SIGNIFY population and that of the Euro Heart Survey of stable angina<sup>23</sup> also highlight the higher risk profile of the SIGNIFY population, as well as changes in contemporary background treatments in the decade since that survey was performed.

An important feature of SIGNIFY is that it is designed to test prospectively the concept of titration of heart rate lowering therapy to a predefined heart rate target of 60 bpm. The target of 60 bpm was selected as it is well established to prevent ischemia and is currently included in guidelines for the prevention of ischemia and angina in patients with stable CAD.<sup>8</sup> Other studies have suggested a better prognosis in CAD patients achieving heart rates of 55-60 bpm.<sup>12</sup> SIGNIFY is therefore setting out to explore questions surrounding which level of heart rate requires treatment, and what should be changed in the management of patients with stable CAD to improve their prognosis.

The primary endpoint of SIGNIFY, a composite of cardiovascular death or nonfatal MI, is noteworthy in view of the strong relationship between heart rate and MI. The results are therefore expected to shed further light on the role of heart rate in the underlying pathophysiology of CAD, as well as the role of pharmacological heart rate lowering with the  $I_f$  inhibitor ivabradine in patients with stable CAD and no signs of heart failure.

The SIGNIFY trial is currently ongoing. This event-driven trial is expected to end in 2014.

## **Acknowledgements**

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## **Appendix**

### **Executive Committee**

K. Fox (Chair, London, UK), R. Ferrari (Co-chair, Ferrara, Italy), I. Ford (Glasgow, UK), P.G. Steg (Paris, France), J-C. Tardif (Montreal, Canada), M. Tendera (Katowice, Poland)

### **Steering Committee**

R. Ferrari (Chair, Ferrara, Italy), R. Iglesias (Argentina), P.A. Zelveian (Armenia), B. Freedman (Australia), K. Huber (Austria), J-L.Vanoverschelde (Belgium), L.A. Machado Cesar (Brazil), N. Gotcheva (Bulgaria), P. L'Allier (Canada), D.Y. Hu (China), C.P. Lau (Hong Kong), M. Bergovec (Croatia), J. Hradec (Czech Republic), P. Clemmensen and P. Hildebrandt (Denmark), J. Eha (Estonia), M. Laine (Finland), N. Danchin (France), S. Kedev (FYROM), V. Chumburidze (Georgia), T. Münzel (Germany), P. Vardas (Greece), J. Borbola (Hungary), R. Kasliwal (India), P. Crean (Ireland), L. Tavazzi (Italy), T.Z. Seisembekov (Kazakhstan), K.B. Seung (Korea), A. Erglis (Latvia), A. Laucevicius (Lithuania), A. Rosli (Malaysia), E. Alexanderson (Mexico), D. Atar (Norway), R. Sy (Philippines), A. Rynkiewicz (Poland), R. Seabra-Gomes (Portugal), C. Macarie (Romania), V.Y. Mareev and Y.A. Karpov (Russia), M. Ostojic (Serbia), T. Koh (Singapore), J. Murin (Slovakia), P. Rakovec (Slovenia), P. Sareli (South Africa), C. Macaya (Spain), M. Dellborg (Sweden), T. Lüscher (Switzerland), C.E. Chiang (Taiwan), P. Srtitara (Thailand), W.H. Van Gilst and J.W. Jukema (The Netherlands), O. Ergene (Turkey), A. Parkhomenko (Ukraine), A. Hall (UK), F. Kuster (Uruguay), N.V. Pham (Vietnam).

Investigators are listed in the supplementary material.

### **Endpoint Validation Committee**

K. Thygesen (Chair, Aarhus, Denmark), M. Frenneaux (Aberdeen, UK), G. Jondeau (Paris, France), A. Mosterd (Amersfoort, The Netherlands)

**Data Monitoring Committee**

J. Camm (Chair, London, UK), G. Murray (Statistician, Edinburgh, UK), H. Dargie (Glasgow, UK), J. Kjekshus (Oslo, Norway), A.P. Maggioni (Florence, Italy)

**List of supplementary material**

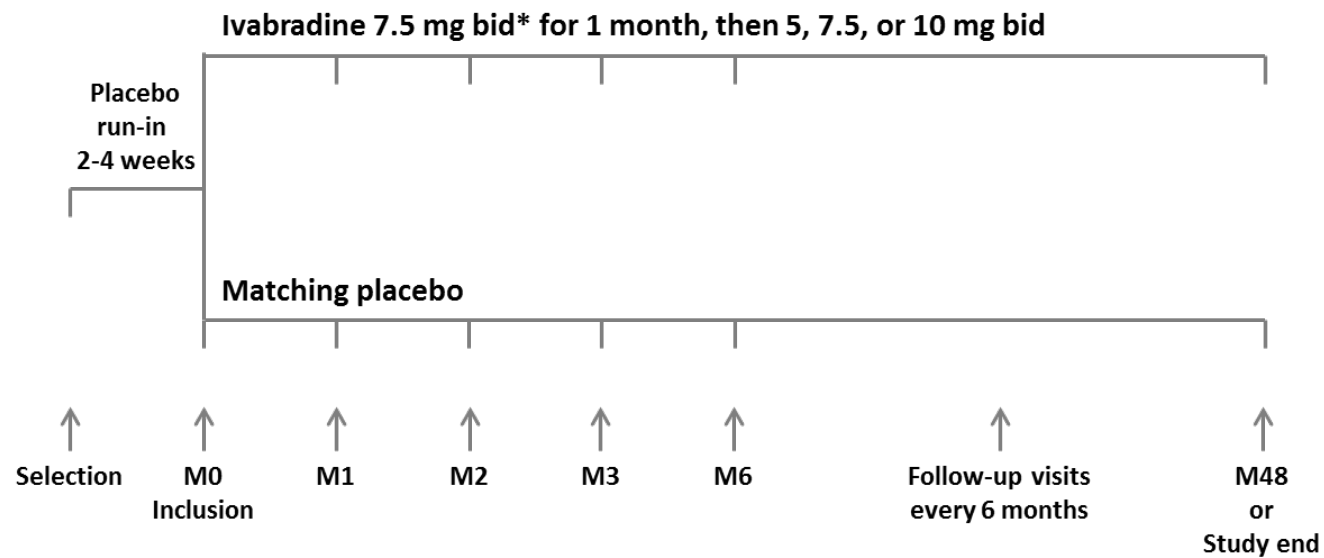
**Supplementary material 1.** Definitions of study endpoints.

**Supplementary material 2.** List of investigators.

**Figure 1.** Study design.

\*Patients aged  $\geq 75$  years were initiated at 5 mg bid.

CCS, Canadian Cardiovascular Society. NYHA, New York Heart Association.



#### Investigation schedule

At every visit:

- Clinical examination, concomitant treatments, and compliance
- Resting heart rate, CCS class, NYHA class, supine blood pressure
- Adverse events

At baseline

- Medical history, left ventricular ejection fraction (echocardiography)

At yearly intervals

- Smoking habits

At baseline, 3 and 12 months,  
and then yearly intervals

- Laboratory parameters (blood sample)

**Table 1.** Main inclusion and exclusion criteria in the SIGNIFY study.

Inclusion criteria
<ul style="list-style-type: none"> <li>• Male or female, aged <math>\geq 55</math> years</li> <li>• Evidence for coronary artery disease: <ul style="list-style-type: none"> <li>▪ Previous myocardial infarction (<math>\geq 3</math> months); or</li> <li>▪ Evidence for multivessel disease irrespective of revascularization status (last coronary revascularization <math>\geq 3</math> months if any); or</li> <li>▪ Evidence for non-revascularized single-vessel disease with a positive non-invasive stress test, or hospital discharge with documented unstable angina 1 to 12 months previously</li> </ul> </li> <li>• In sinus rhythm, with resting heart rate <math>\geq 70</math> bpm (standard 12-lead electrocardiogram)</li> <li>• Without left ventricular systolic dysfunction (left ventricular ejection fraction <math>&gt; 40\%</math>)</li> <li>• Ambulatory patients in a stable condition with respect to angina (<math>\geq 1</math> month) and on appropriate and stable doses of conventional cardiovascular medication (<math>\geq 1</math> month)</li> <li>• Additional cardiovascular risk factors <ul style="list-style-type: none"> <li>▪ <u>At least one major</u> cardiovascular risk factor: <ul style="list-style-type: none"> <li>○ Angina pectoris in Canadian Cardiovascular Society class II or higher (<math>\geq 1</math> month); or</li> <li>○ Objective evidence of myocardial ischemia with moderate to large deficit induced by noninvasive stress testing (<math>\leq 12</math> months) in patients who did not undergo subsequent revascularization; or</li> <li>○ Hospital discharge after a major coronary event <math>\leq 12</math> months (acute myocardial infarction <math>\geq 3</math> months, or unstable angina <math>\geq 1</math> month)</li> </ul> </li> <li>▪ Or <u>at least two minor</u> cardiovascular risk factors: <ul style="list-style-type: none"> <li>○ Low high-density lipoprotein cholesterol (<math>&lt; 40</math> mg/dL); and/or high low-density lipoprotein cholesterol (<math>&gt; 160</math> mg/dL despite lipid-lowering treatment); or</li> <li>○ Type 1 or 2 diabetes mellitus; or</li> <li>○ Peripheral artery disease; or</li> <li>○ Current smoker (<math>\geq 10</math> cigarettes per day); or</li> <li>○ Age <math>\geq 70</math> years</li> </ul> </li> </ul> </li> <li>• Informed consent</li> </ul>
Exclusion criteria
<ul style="list-style-type: none"> <li>• Recent myocardial infarction, coronary revascularization, stroke, or transient ischemic attack (<math>\leq 3</math> months); or with a transplanted heart, implanted pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy</li> <li>• Scheduled for coronary revascularization; or likely to require surgery for valvular disease</li> <li>• Permanent atrial fibrillation or flutter</li> <li>• Sick sinus syndrome, sinoatrial block, congenital long QT, 2nd degree and complete atrioventricular block.</li> <li>• Severe or uncontrolled hypertension; or hypotension</li> <li>• Heart failure (New York Heart Association class II or higher, or hospitalization for heart failure <math>\leq 12</math> months)</li> <li>• Requirement for treatments prohibited during the study</li> <li>• Current treatment with ivabradine, or known hypersensitivity to ivabradine</li> <li>• Abnormal serum creatinine (<math>&gt; 200</math> <math>\mu\text{mol/L}</math>), transaminases (<math>&gt; 3 \times \text{ULN}</math>), or hemoglobin (men, <math>&lt; 110</math> g/L, or women, <math>&lt; 100</math> g/L)</li> </ul>



**Table 2.** Baseline characteristics

Values are means±SD or n (%).

ACE, angiotensin converting enzyme. CCB, calcium channel blocker. CCS, Canadian Cardiovascular Society. MRA, mineralocorticoid receptor antagonist. NYHA.

	Whole population (N=19 102)		Whole population (N=19 102)
<b>Demographic characteristics</b>			
Age (years)	65.0±7.2	Ethnic origin	
• <70 years	13 669 (72%)	• Caucasian	15 533 (81%)
• ≥70 years	5433 (28%)	• Asian	2547 (13%)
• ≥75 years	2228 (12%)	• Other	1021 (5%)
Body mass index (kg/m <sup>2</sup> )	28.8±4.6	Systolic blood pressure (mm Hg)	130.5±13.6
Heart rate (bpm)	77.2±7.0	Diastolic blood pressure (mm Hg)	78.2±8.2
Male	13 840 (72%)		
<b>Cardiovascular risk factors and medical history</b>			
Coronary artery disease duration (years)	6.1±6.3	Dyslipidemia (%)	13 622 (71%)
Previous myocardial infarction	13 986 (73%)	Diabetes mellitus (%)	8216 (43%)
Previous coronary revascularization	12 882 (67%)	Peripheral artery disease (%)	3963 (21%)
Angina status		Current smoker (%)	4610 (24%)
• No angina symptoms	4812 (25%)	Hypertension (%)	16 409 (86%)
• CCS class I	2241 (12%)	Left ventricular ejection fraction (%)	56.5±8.6
• CCS class II to IV	12 049 (63%)	Stroke (%)	1245 (7%)
<b>Concomitant treatments</b>			
Antithrombotic agents	18 646 (98%)	Calcium channel blockers	5864 (31%)
Statins	17570 (92%)	Diuretics (excluding MRA)	5769 (30%)
Beta-blockers	15 873 (83%)	MRA	936 (5%)
ACE inhibitors	11 318 (59%)	Organic nitrates	7560 (40%)
Angiotensin II receptor blockers	4469 (23%)	Antidiabetic agents	7571 (40%)